## REMARKS

**Amendment to the Claims.**

Applicant has amended the claims to more clearly state the Applicant's invention.

Claims 63 to 70 are new, and are dependent on either independent claim 41 or 50. These claims are directed to the compositions of independent claims 41 and 50 further comprising a metal ion complexed to the metal ion-binding domain.

Claims 71 to 81 are new, with claim 71 being a new independent claim. Claim 71 is directed to an alternative method of claiming the library, based on a library of compounds of the formula $R_1$-X-$R_2$ wherein a metal ion is complexed to X. The same is disclosed at, inter alia, page 17, line 28 through page 18; page 26, line 19 through page 27, line 4; and page 57, line 16 through page 65, line 25.

**Response to Examiner's Preliminary Remarks.**

Applicant acknowledges the election to Group II, claims 41-59, and the withdrawal of claims 35-40 and 60-62 from further consideration. The claims at issue are claims 41-59.

With respect to the statement that the oath or declaration is defective, Applicant notes that a new declaration was filed concurrent with the application, showing an execution date by the inventor of December 29, 1999, and that this declaration specifically claimed priority to S.N. 08/660,697, filed June 5, 1996. While the declaration filed in S.N. 08/660,697 claimed priority to S.N. 08/476,652, the declaration filed in this case, application S.N. 09/483,837, correctly and specifically claimed priority only to S.N. 08/660,697, filed June 5, 1996. A copy of the declaration with an execution date by the inventor of December 29, 1999 is attached hereto as Attachment A, to assist the Examiner in locating the declaration filed with this application. In any event, Applicant will file a supplemental declaration upon allowance of claims.

**Claim Rejections - 35 U.S.C. § 101.**

Claims 41-59 are rejected under 35 U.S.C. § 101 on the grounds that the claimed invention is not new or useful. For the following reasons, Applicant respectfully traverses this rejection.

Independent claims 41 and 50 have been amended, as set forth above, to provide that the library members comprise a sequence of no more than "about twenty amino acid residues." It is submitted that this limitation excludes, for example, naturally occurring catalytic antibodies. Further, claim 41 is limited to "a sequence of three or more amino acid residues, mimics of amino acid residues or combinations thereof, bound to solid phase characterized by . . . a cleavable bond attaching the sequence to solid phase . . ." Applicant respectfully notes that this limitation additionally excludes the claimed combinatorial library from, e.g., reading on naturally occurring catalytic antibodies.

To the extent that the 35 U.S.C. § 101 rejection is based on an assertion that the invention is not supported by either a specifically asserted utility or a well-established utility, Applicant respectfully traverses this argument for the reasons set forth below with respect to the 35 U.S.C. § 112 rejection.

**Claim Rejections - 35 U.S.C. § 112, First Paragraph.**

On page 4, first full paragraph, of the Office Action, the Examiner rejected claims 41-59 under 35 U.S.C. § 112, first paragraph, because the claimed invention is not support by either a specifically support utility or a well established utility. For the reasons set forth below, Applicant respectfully traverses this ground of rejection, together with the parallel rejection under 35 U.S.C. § 101.

Based upon the specification and prior art of record, the utility of combinatorial libraries is both disclosed and well-established. The Examiner states that the specification asserts the utility of the combinatorial library for "screening." (Office Action page 3, third paragraph) While "screening", in the sense of assays to determine biological activity or receptor specificity, is a procedure frequently employed with combinatorial libraries, the utility of combinatorial libraries is not for "screening" as such. Rather, the utility is to select and identify metallopeptides and metallo-constructs, which as disclosed by Applicant

have a highly constrained structure (see page 57, lines 24-27), which bind to receptors of interest, and which may be accordingly selected. The application accordingly discloses use of libraries directed toward integrin receptors that recognize the RGD sequence (page 59, line 1 and following); tuftsin receptors (page 60, line 22 and following); peptide hormone receptors, such as somaotstatin, cholecystokinin, opioid, melanotropin, LHRH, tachykinin and similar peptide hormone receptors (page 62, line 11 and following); and so on. It is further submitted that the use and utility of combinatorial libraries is well known in the art; see the discussion and literature cited at page 9, line 18 through page 15, line 6 and at page 64, line 16 through page 65, line 25. Further, Applicant notes that the Patent and Trademark Office has consistently recognized the inherent utility of combinatorial libraries *per se*, and has issued numerous patents wherein the claims are directly solely to combinatorial libraries. See, e.g., U.S. Patent Nos. 6,194,544, 6,025,371, 5,859,190, 5,824,483, 6,127,381 and 5,766,963. With respect to the Examiner's comment regarding "screening", it is noted that U.S. Patent No. 5,766,963 is drawn to a library "for biological screening".

It is further submitted that "one skilled in the art" would know how to use a combinatorial library as claimed. The use of combinatorial libraries is well known in the art; see, e.g., the discussion and literature cited at page 9, line 18 through page 15, line 6 and at page 64, line 16 through page 65, line 25. It is noted that Applicant has specifically incorporated by reference all patents and publications cited in the specification. Page 127, lines 19-21.

On page 4, first full paragraph, of the Office Action, the Examiner rejected claims 41-59 under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for libraries that bind to rhenium metal, does not reasonably provide enablement for any type of combinatorial library with at least three residues, two of which form a metal ion-binding domain. Applicant respectfully traverses this rejection. At the outset, it is noted that binding to technetium (both $Tc^{99m}$ and $Tc^{99}$) is specifically disclosed

throughout the specification, and that such metal ions could accordingly be applied to the library using the teachings relating to technetium. However, the specification adequately discloses to one of skill in the art the use of a wide variety of metals. See Examples 65 and 66, page 123, relating to tetradentate metal ions such as Cu, Co, Zn, Ni or Mn; the background discussion on peptide-metal ion interaction at page 7, line 3 through page 9, line 17; page 37, line 26 through page 38, line 19, disclosing medically use metal ions; page 40, line 24 through page 42, line 11, disclosing coordination of metal ions, and specifically tetradentate to hexadentate coordination spheres; page 42, line 12 through page 46, line 25, disclosing complexation with a variety of metal ions. Note particularly the references cited at page 43, lines 12-22, dealing with metal ion complexation of penta- or hexadentate or higher coordination spheres in peptides. Such references disclose additional information to one skilled in the art, and are incorporated by reference.

On page 5, first full paragraph, of the Office Action, the Examiner rejected claims 41-59 under 35 U.S.C. § 112, first paragraph, because the "scope of enabling disclosure ... is not commensurate in scope with the broadly, incompletely identified components of the claimed library." Applicant respectfully traverses this rejection. The Examiner notes a single example in the specification, Example 67, for this ground of rejection. To the extent that Examiner asserts that "conditions necessary for the bioassays" must be disclosed, Applicant respectfully disagrees. Bioassays and various methods of screening and elucidating a "hit" are well known in the art of combinatorial chemistry. See, for example, the discussion and literature cited at page 9, line 18 through page 15, line 6 and more specifically at page 64, line 16 through page 65, line 25. The disclosure at page 64 and following specifically discloses screening to identify one or more receptor-binding or pharmacologically-active candidates by techniques reported in the prior art. These assay and related methods are specifically described (e.g., direct target binding approaches, deconvolution and iterative resynthesis approaches, orthogonal pools of two co-synthesized libraries, positional scanning methods and combinations thereof). Specific prior art articles are cited for

each of the methods, which prior art references are incorporated into the specification by reference. Further, the specification discloses a number of bioassays that could obviously be employed with a combinatorial library; see, e.g., Example 11 on page 89 (binding to fresh platelets), Example 12 on page 90 (binding to fixed platelets), Example 28 (binding to clots), Example 28 (binding to human PMN cells), Example 29 (binding to HL-60 cells) and Example 43 (a nitroblue tetrazolium dye reduction assay).

**Claim Rejections - 35 U.S.C. § 112, Second Paragraph.**

On page 5, second and following paragraphs, certain claims were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection on the following grounds.

The phrase "synthesized on solid phase" appears in the preamble of claim 41. It describes not a "method of synthesis" but rather characterizes and limits the library of the invention. That is, in a) the sequences are limited as "bound to sold phase". Thus the library itself consists of "different sequence peptide or peptidomimetic members" which are characterized, in part, as "bound to solid phase". That this is also the method employed does not detract from the proper characterization of the library.

The phrase "forming a metal ion-binding domain" characterizes a specific portion of the sequence, and does not relate to a "method of synthesis" as claimed by Examiner. Rather, this describes a functional characteristic, i.e., that the sequence can bind to a metal ion. In any event, this phrase has been amended as discussed below.

The phrase "cleavable bond attaching the sequence to solid phase" characterizes the library, which consists to library members "bound to solid phase", the binding being by "a cleavable bond attaching the sequence to solid phase." That is, a limitation of the claim is the "cleavable bond" itself. A Boc group, for example, is commonly employed and cleavable.

The term "unique" is, it is submitted, as clear as is permitted in the English language. The limitation is " a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof." Thus unique may be either a unique selection (e.g., amino acid sequences G-G-G-C-A versus G-G-G-C-T, where each is clearly unique with respect to the other) or a unique sequence (e.g., amino acid sequences G-G-G-C-A and A-G-G-G-C are unique sequences, even though the amino acids are the same in each sequence). This thus clearly provides a limitation relating to the difference between the "different sequence peptide ... members", that is, that each member has either a unique selection of amino acids or mimics, or a unique sequence of amino acids or mimics.

The term "domain" is, it is submitted, as clear as is permitted in the English language. However, Applicant has amended the claims to recite "backbone for complexing with a metal ion" in lieu of "domain". It is noted that the term "metal ion-binding backbone for complexing with a metal ion" was employed in the claims of the parent application, U.S. Patent No. 6,027,711, of which the instant application is a divisional, and the grandparent application, U.S. Patent No. 5,891,418.

The Applicant notes that a "sequence" of one is indefinite, and has amended the claims to delete the same.

With respect to claim 45 and 46 and 54 and 55, and the word "removable", the conventional art term "cleavable" has been substituted.

With respect to use of abbreviations, "Trt" has been spelled out as "trityl."

With respect to claims 47 and 48 and claims 56 and 57, the claims have been amended to address the concerns raised by the Examiner with respect to "outside" and "diversity."

**Claim Rejections - 35 U.S.C. §§ 102 and 103.**

Claims 41, 45, 46, 47, 50, 54, 55 and 59 were rejected under 35 U.S.C. § 102(a) as anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over, Francis et al [(J.Am.Chem.Soc.) (I) or

Current Opinion in Chemical Biol. (II)]. For the reasons set forth below, Applicant respectfully traverses this rejection.

*Francis I and II Are Not Prior Art.* The specification on which this application is based was S.N. 08/660,697, filed June 5, 1996. Francis II was published in 1998. Francis I was published 18 September 1996 (see Information Disclosure Statement by Applicant listing the publication date; see also Attachment B hereto). There is no basis for a rejection under either 35 U.S.C. § 102(a) or 35 U.S.C. § 103. See, e.g., MPEP § 706.02(a). As provided in MPEP § 706.02(a), for § 102(a) to apply, the "reference must have a publication date earlier in time than the effective filing date of the application." The references do not. Accordingly, these references may not properly be applied.

*Kay Neither Anticipates Nor Renders Obvious the Claims.* Kay teaches a phage display library. Claim 41 is to a library wherein members are bound to solid phase, and is thus clearly distinguishable. The cited reference, at col. 47, line 55 and following, shows screening to a metal ion where the metal ion is immobilized "in a tridentate fashion" utilizing a form of immobilized metal affinity chromatography (see col. 47, lines 62-67 as to zinc, and col. 50, lines 31-33 as to copper and nickel). By contrast, the library of claims 41 and 50 are to peptides which may be bound to metal ion in solution. Further, claims 41 and 50 have been amended to incorporate the limitation of claims 42 and 51, whereby at least one residue has at least one sulfur available for binding; Kay teaches only use of His groups (col. 50, lines 7-30) and specifically provides that Cys may not be employed in his disclosed library (col. 48, line 66 bridging col. 49, line 25).

**Conclusion**

In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

If any issues remain, or if the Examiner believes that prosecution of this application might be expedited by discussion of the issues, she is cordially invited to telephone the undersigned attorney for Applicant at the telephone number listed below.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached paper is captioned "**Version with Markings to Show Changes Made**."

A check for additional claim fees is attached. Also being filed herewith is a Petition for Extension of Time to July 14, 2001, with the appropriate fee. Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

Dated: July 16, 2001

By: _____
Stephen A. Slusher, Reg. No. 43,924
Direct line: (505) 998-6130

PEACOCK, MYERS & ADAMS, P.C.
Attorneys for Applicant(s)
P.O. BOX 26927
Albuquerque, New Mexico 87125-6927

Telephone: (505) 998-1500
Facsimile: (505) 243-2542

**Customer No. 005179**

File: 70025-9902
[I:\AMDS\Palatin-Midas\MIDAS Combinatorial '837 OA RESPONSE.doc]

**Version with Markings to Show Changes Made**

41. A combinatorial library of different sequence peptide or peptidomimetic members synthesized on solid phase, where each constituent library member comprises:

(a) a sequence of between three and about twenty [or more] amino acid residues, mimics of amino acid residues or combinations thereof, bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof, forming a metal ion-binding [domain] backbone for complexing with a metal ion and comprising at least one residue with at least one sulfur available for binding to a metal ion in solution, (ii) [a sequence of] one or more amino acid residues, mimics of amino acid residues or combinations thereof, at the N- or C- terminus of the metal ion-binding [domain] backbone, or at both the N- and C-terminus of the metal ion-binding [domain] backbone, and (iii) a cleavable bond attaching the sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof.

43. The combinatorial library of claim [42] 41 wherein the metal ion-binding [domain] backbone further comprises at least one residue with at least one nitrogen available for binding to a metal ion.

44. The combinatorial library of claim [42] 41 wherein the metal ion-binding [domain] backbone comprises three residues forming an $N_3S_1$ metal ion complexation group.

45. The combinatorial library of claim [42] 41 wherein the at least one sulfur is protected by a [removable] cleavable S-protecting group.

46. The combinatorial library of claim 45 wherein the [removable] cleavable S-protecting group is [Trt] trityl.

47. The combinatorial library of claim 41 wherein the [diversity in the sequence] unique selection or sequence occurs in the metal ion-binding [domain] backbone.

48. The combinatorial library of claim 41 wherein the [diversity in the sequence] unique selection or sequence occurs [outside the metal ion-binding domain] in the one or more amino acid residues, mimics of amino acid residues or combinations thereof, at the N- or C- terminus of the metal ion-binding backbone, or at both the N- and C-terminus of the metal ion-binding backbone.

49. The [solid phase] combinatorial library of claim [42] 41 wherein the at least one residue containing at least one sulfur available for binding to a metal ion is L- or D-cysteine; L- or D-penicillamine; L- or D-homocysteine; 2'-mercapto-tryptophan; $N^{\beta}$-(2 mercaptoethane)-α,β-diaminopropionic acid; 2-mercaptoethylamine; thioglycolic acid; mercaptoproprionic acid; 2-mercaptoaniline; or 2-mercaptosuccinic acid.

50. A combinatorial library of different sequence peptide or peptidomimetic members synthesized in solution, where each constituent library member comprises:

(a) a sequence of [a combination of] between three and about twenty [or more] amino acid residues and mimics of amino acid residues in solution characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding [domain] backbone for complexing with a metal ion and comprising at least one residue with at least one sulfur available for binding to a metal ion in solution, and (ii) [a sequence of] one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C- terminus of the metal ion-binding [domain] backbone, or at both the N- and C-terminus of the metal ion-binding [domain] backbone; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof.

52. The combinatorial library of claim [51] 50 wherein the metal ion-binding [domain] backbone further comprises at least one residue with at least one nitrogen available for binding to a metal ion.

53. The combinatorial library of claim [52] 50 wherein the metal ion-binding [domain] backbone comprises three residues forming an $N_3S_1$ metal ion complexation group.

54. The combinatorial library of claim 50 wherein the at least one sulfur is protected by a [removable] cleavable S-protecting group.

55. The combinatorial library of claim 54 wherein the [removable] cleavable S-protecting group is [Trt] trityl.

56. The combinatorial library of claim 50 wherein the [diversity in the sequence] unique selection or sequence occurs in the metal ion-binding [domain] backbone.

57. The combinatorial library of claim 50 wherein the [diversity in the sequence] unique selection or sequence occurs [outside the metal ion-binding domain] in the one or more amino acid residues, mimics of amino acid residues or combinations thereof, at the N- or C- terminus of the metal ion-binding backbone, or at both the N- and C-terminus of the metal ion-binding backbone.

58. The combinatorial library of claim [51] 50 wherein the at least one residue containing at least one sulfur available for binding to a metal ion is L- or D-cysteine; L- or D-penicillamine; L- or D-homocysteine; 2'-mercapto-tryptophan; $N^{\beta}$-(2 mercaptoethane)-α,β-diaminopropionic acid; 2-mercaptoethylamine; thioglycolic acid; mercaptoproprionic acid; 2-mercaptoaniline; or 2-mercaptosuccinic acid.

59. The combinatorial library of claim 50 wherein each constituent library member further comprises a metal ion complexed to the metal ion-binding [domain] backbone.

--63. The combinatorial library of claim 41, wherein each constituent library member further comprises a metal ion complexed to the metal ion-binding backbone.

64. The combinatorial library of claim 63, wherein the metal ion is selected from the group of metals consisting of technetium and rhenium.

65. The combinatorial library of claim 44, further comprising a metal ion complexed to the $N_3S_1$ metal ion complexation group.

66. The combinatorial library of claim 65, wherein the metal ion is selected from the group of metals consisting of technetium and rhenium.

67. The combinatorial library of claim 50, further comprising a metal ion complexed to the metal ion-binding domain.

68. The combinatorial library of claim 67, wherein the metal ion is selected from the group of metals consisting of technetium and rhenium.

69. The combinatorial library of claim 52, further comprising a metal ion complexed to the $N_3S_1$ metal ion complexation group.

70. The combinatorial library of claim 69, wherein the metal ion is selected from the group of consisting of technetium and rhenium.

71. A combinatorial library comprising compounds of the structure:

$R_1$-X-$R_2$

wherein X is a complexing backbone for complexing a metal ion comprising between two and four amino acids, wherein at least two amino acids are contiguous and at least one residue comprises at least one sulfur available for binding to a metal ion, so that substantially all of the valences of the metal ion are satisfied upon complexation of the metal ion with X;

wherein $R_1$ and $R_2$ each comprise from 0 to about 20 amino acids; and

a metal ion complexed to X;

wherein $R_1$-X-$R_2$ has a conformationally constrained secondary structure comprising at least a part of X and at least a part of $R_1$ or $R_2$.

72. The combinatorial library of claim 71, wherein the metal ion is an ionic form of the element selected from the group consisting of iron, cobalt, nickel, cooper, zinc, manganese, arsenic, selenium, technetium, ruthenium, palladium, silver, cadmium, indium, antimony, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, bismuth, polonium or astatine.

73. The combinatorial library of claim 71, wherein the metal ion is selected from the group of consisting of technetium and rhenium.

74. The combinatorial library of claim 71, wherein the at least one residue containing at least one sulfur available for binding to a metal ion is L- or D-cysteine; L- or D-penicillamine; L- or D-homocysteine; 2'-mercapto-tryptophan; $N^{\beta}$-(2 mercaptoethane)-α,β-diaminopropionic acid; 2-mercaptoethylamine; thioglycolic acid; mercaptoproprionic acid; 2-mercaptoaniline; or 2-mercaptosuccinic acid.

75. The combinatorial library of claim 71 wherein X comprises at least one residue with at least one nitrogen available for binding to a metal ion.

76. The combinatorial library of claim 71 wherein X is three residues forming an $N_3S_1$ metal ion complexing backbone.

77. The combinatorial library of claim 71, wherein the conformationally constrained secondary structure is a specific regional secondary structure which is a mimic of a reverse turn structure.

78. The combinatorial library of claim 71, wherein if less than all of the valences of the metal ion are otherwise satisfied upon complexation of the metal ion with the amino acids comprising X, then X also comprises a derivatized amino acid or spacer sequence, which derivatized amino acid or spacer sequence comprises at least one nitrogen, sulfur or oxygen atom available for complexing with the available valences of the metal ion, so that all of said valences of the metal ion are satisfied upon complexation of the metal ion with X.

79. The combinatorial library of claim 71, wherein the compounds of the structure $R_1$-X-$R_2$ are linear peptides complexed to a metal ion.

80. The combinatorial library of claim 71, wherein each of $R_1$ and $R_2$ comprise at least one amino acid, and further wherein $R_1$ and $R_2$ are joined by a cyclic bridge, whereby $R_1$-X-$R_2$ are cyclic peptides complexed to a metal ion.

81. The combinatorial library of claim 71, wherein the compounds of the structure $R_1$-X-$R_2$ are bound to solid phase.--

## CLAIMS

What is claimed is:

41. (Amended) A combinatorial library of different sequence peptide or peptidomimetic members synthesized on solid phase, where each constituent library member comprises:

(a) a sequence of between three and about twenty amino acid residues, mimics of amino acid residues or combinations thereof, bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof, forming a metal ion-binding backbone for complexing with a metal ion and comprising at least one residue with at least one sulfur available for binding to a metal ion in solution, (ii) one or more amino acid residues, mimics of amino acid residues or combinations thereof, at the N- or C- terminus of the metal ion-binding backbone, or at both the N- and C-terminus of the metal ion-binding backbone, and (iii) a cleavable bond attaching the sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof.

43. (Amended) The combinatorial library of claim 41 wherein the metal ion-binding backbone further comprises at least one residue with at least one nitrogen available for binding to a metal ion.

44. (Amended) The combinatorial library of claim 41 wherein the metal ion-binding backbone comprises three residues forming an $N_3S_1$ metal ion complexation group.

45. (Amended) The combinatorial library of claim 41 wherein the at least one sulfur is protected by a cleavable S-protecting group.

46. (Amended) The combinatorial library of claim 45 wherein the cleavable S-protecting group is trityl.

47. (Amended) The combinatorial library of claim 41 wherein the unique selection or sequence occurs in the metal ion-binding backbone.

48. (Amended) The combinatorial library of claim 41 wherein the unique selection or sequence occurs in the one or more amino acid residues, mimics of amino acid residues or combinations thereof, at the N- or C- terminus of the metal ion-binding backbone, or at both the N- and C-terminus of the metal ion-binding backbone.

49. (Amended) The combinatorial library of claim 41 wherein the at least one residue containing at least one sulfur available for binding to a metal ion is L- or D-cysteine; L- or D-penicillamine; L- or D-homocysteine; 2'-mercapto-tryptophan; $N^{\beta}$-(2 mercaptoethane)-α,β-diaminopropionic acid; 2-mercaptoethylamine; thioglycolic acid; mercaptoproprionic acid; 2-mercaptoaniline; or 2-mercaptosuccinic acid.

50. (Amended) A combinatorial library of different sequence peptide or peptidomimetic members synthesized in solution, where each constituent library member comprises:

(a) a sequence of between three and about twenty amino acid residues and mimics of amino acid residues in solution characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding backbone for complexing with a metal ion and comprising at least one residue with at least one sulfur available for binding to a metal ion in solution, and (ii) one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C- terminus of the metal ion-binding backbone, or at both the N- and C-terminus of the metal ion-binding backbone; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof.

52. (Amended) The combinatorial library of claim 50 wherein the metal ion-binding backbone further comprises at least one residue with at least one nitrogen available for binding to a metal ion.

53. (Amended) The combinatorial library of claim 50 wherein the metal ion-binding backbone comprises three residues forming an $N_3S_1$ metal ion complexation group.

54. (Amended) The combinatorial library of claim 50 wherein the at least one sulfur is protected by a cleavable S-protecting group.

55. (Amended) The combinatorial library of claim 54 wherein the cleavable S-protecting group is trityl.

56. (Amended) The combinatorial library of claim 50 wherein the unique selection or sequence occurs in the metal ion-binding backbone.

57. (Amended) The combinatorial library of claim 50 wherein the unique selection or sequence occurs in the one or more amino acid residues, mimics of amino acid residues or combinations thereof, at the N- or C- terminus of the metal ion-binding backbone, or at both the N- and C-terminus of the metal ion-binding backbone.

58. (Amended) The combinatorial library of claim 50 wherein the at least one residue containing at least one sulfur available for binding to a metal ion is L- or D-cysteine; L- or D-penicillamine; L- or D-homocysteine; 2'-mercapto-tryptophan; $N^{\beta}$-(2 mercaptoethane)-α,β-diaminopropionic acid; 2-mercaptoethylamine; thioglycolic acid; mercaptoproprionic acid; 2-mercaptoaniline; or 2-mercaptosuccinic acid.

59. (Amended) The combinatorial library of claim 50 wherein each constituent library member further comprises a metal ion complexed to the metal ion-binding backbone.

--63. The combinatorial library of claim 41, wherein each constituent library member further comprises a metal ion complexed to the metal ion-binding backbone.

64. The combinatorial library of claim 63, wherein the metal ion is selected from the group of metals consisting of technetium and rhenium.

65. The combinatorial library of claim 44, further comprising a metal ion complexed to the $N_3S_1$ metal ion complexation group.

66. The combinatorial library of claim 65, wherein the metal ion is selected from the group of metals consisting of technetium and rhenium.

67. The combinatorial library of claim 50, further comprising a metal ion complexed to the metal ion-binding domain.

68. The combinatorial library of claim 67, wherein the metal ion is selected from the group of metals consisting of technetium and rhenium.

69. The combinatorial library of claim 52, further comprising a metal ion complexed to the $N_3S_1$ metal ion complexation group.

70. The combinatorial library of claim 69, wherein the metal ion is selected from the group of consisting of technetium and rhenium.

71. A combinatorial library comprising compounds of the structure:

$R_1$-X-$R_2$

wherein X is a complexing backbone for complexing a metal ion comprising between two and four amino acids, wherein at least two amino acids are contiguous and at least one residue comprises at least one sulfur available for binding to a metal ion, so that substantially all of the valences of the metal ion are satisfied upon complexation of the metal ion with X;

wherein $R_1$ and $R_2$ each comprise from 0 to about 20 amino acids; and

a metal ion complexed to X;

wherein $R_1$-X-$R_2$ has a conformationally constrained secondary structure comprising at least a part of X and at least a part of $R_1$ or $R_2$.

72. The combinatorial library of claim 71, wherein the metal ion is an ionic form of the element selected from the group consisting of iron, cobalt, nickel, cooper, zinc, manganese, arsenic, selenium, technetium, ruthenium, palladium, silver, cadmium, indium, antimony, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, bismuth, polonium or astatine.

73. The combinatorial library of claim 71, wherein the metal ion is selected from the group of consisting of technetium and rhenium.

74. The combinatorial library of claim 71, wherein the at least one residue containing at least one sulfur available for binding to a metal ion is L- or D-cysteine; L- or D-penicillamine; L- or D-homocysteine; 2'-mercapto-tryptophan; $N^{\beta}$-(2 mercaptoethane)-α,β-diaminopropionic acid; 2-mercaptoethylamine; thioglycolic acid; mercaptoproprionic acid; 2-mercaptoaniline; or 2-mercaptosuccinic acid.

75. The combinatorial library of claim 71 wherein X comprises at least one residue with at least one nitrogen available for binding to a metal ion.

76. The combinatorial library of claim 71 wherein X is three residues forming an $N_3S_1$ metal ion complexing backbone.

77. The combinatorial library of claim 71, wherein the conformationally constrained secondary structure is a specific regional secondary structure which is a mimic of a reverse turn structure.

78. The combinatorial library of claim 71, wherein if less than all of the valences of the metal ion are otherwise satisfied upon complexation of the metal ion with the amino acids comprising X, then X also comprises a derivatized amino acid or spacer sequence, which derivatized amino acid or spacer sequence comprises at least one nitrogen, sulfur or oxygen atom available for complexing with the available valences of the metal ion, so that all of said valences of the metal ion are satisfied upon complexation of the metal ion with X.

79. The combinatorial library of claim 71, wherein the compounds of the structure $R_1$-X-$R_2$ are linear peptides complexed to a metal ion.

80. The combinatorial library of claim 71, wherein each of $R_1$ and $R_2$ comprise at least one amino acid, and further wherein $R_1$ and $R_2$ are joined by a cyclic bridge, whereby $R_1$-X-$R_2$ are cyclic peptides complexed to a metal ion.

81. The combinatorial library of claim 71, wherein the compounds of the structure $R_1$-X-$R_2$ are bound to solid phase. --